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# Cardiac MRI outcomes in patients with Duchenne Muscular Dystrophy treated with delandistrogene moxeparvovec: Findings from EMBARK Part 1

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## What does this study mean for the DMD community?

- Cardiac magnetic resonance imaging (cMRI), a key modality used to evaluate cardiac function in patients with DMD, can identify early signs of cardiac disease progression that are not yet clinically evident.[1,2]
- In the EMBARK study (NCT05096221),[3] cMRI measures at Week 52 post-infusion supported the previously demonstrated manageable safety profile of delandistrogene moxeparvovec, with results indicating no adverse cardiac effects 1 year post-treatment.

## Conclusions

- At Week 52 post-administration with delandistrogene moxeparvovec, there were no signs of alterations in cardiac measures compared with placebo based on cardiac function, volume or mass evaluated by non-contrast cMRI.
- Results indicated no adverse cardiac effects 1 year after treatment, supporting the previously demonstrated manageable safety profile of delandistrogene moxeparvovec in clinical trial settings.
- Cardiac safety and efficacy will continue to be assessed longer-term in these patients.

## OBJECTIVE

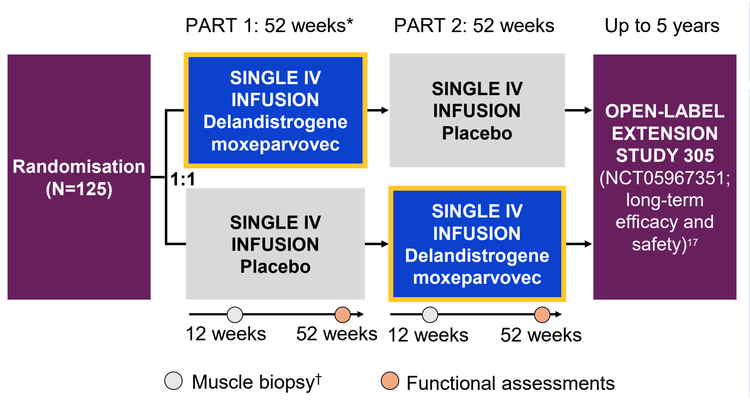
- We report results of a pre-specified, exploratory analysis in a subset of patients (n=39) who underwent non-contrast cMRI in EMBARK Part 1 (baseline and Week 52) to evaluate the effect of delandistrogene moxeparvovec on cardiac function, volume and mass.

## BACKGROUND

- DMD is a rare, X-linked neuromuscular disease caused by pathogenic variants in the *DMD* gene that result in the absence of functional dystrophin and continuous muscle damage, beginning from birth.[4,5]
  - Absent functional dystrophin causes progressive myocardial fibrosis, initially presenting as subclinical cardiomyopathy and later progressing to dilated cardiomyopathy and heart failure.[2]
- Delandistrogene moxeparvovec is an rAAVrh74 vector-based gene transfer therapy (with an MHCK7 promoter containing an α-MHC enhancer highly active in cardiac muscle) that delivers a transgene encoding delandistrogene moxeparvovec micro-dystrophin, an engineered, functional form of dystrophin shown to stabilise or slow disease progression in DMD.[4–7]
  - It is approved in the US and in other select countries.[8–14]
- cMRI is a non-invasive method of monitoring cardiac safety and disease progression in DMD, and is sensitive to subclinical cardiac changes.[1,2,15,16]
  - Early alterations in circumferential strain can be detected in patients with DMD aged <10 years who still have normal ejection fractions, even in the absence of late gadolinium enhancement positivity. These alterations progress with age, eventually affecting left ventricle ejection fraction.[16]
- EMBARK, a Phase 3, two-part, multinational, randomised, double-blind, placebo-controlled trial in patients with DMD aged ≥4 to <8 years (**Figure 1**), showed stabilisation of DMD disease progression and manageable safety following delandistrogene moxeparvovec.[17]

## METHODS

### Figure 1. EMBARK study design




**Stratification based on** age at randomisation (≥4 to <6 or ≥6 to <8 years) and NSAA total score at screening (≤22 or >22)

**Key inclusion criteria:**
- Ambulatory males aged ≥4 to <8 years at randomisation
- Confirmed DMD diagnosis (*DMD* mutation fully contained within exons 18–79 [inclusive])
- Able to cooperate with motor assessments
- NSAA total score >16 and <29 points at screening
- TTR <5 seconds at screening
- On a stable daily dose of oral corticosteroids for ≥12 weeks before screening
- rAAVrh74 total binding antibody titres <1:400

*At Week 52, a subset of 39 patients underwent non-contrast cMRI at pre-selected sites per protocol. Sites were pre-selected based on experience in performing routine MRI. †Only a subset of patients received a muscle biopsy for expression assessments, based on site experience and feasibility.

### cMRI analyses

- Prior to each scanning session, patients and parents/guardians were carefully screened for MR compatibility and safety following local screening procedures.
- A pre-specified exploratory cMRI sub-study from EMBARK Part 1 assessed the therapeutic impact of delandistrogene moxeparvovec on non-contrast (to mitigate the risk of adverse events) cMRI markers of disease progression in a subset of patients who received delandistrogene moxeparvovec ($1.33\times10^{14}$ vg/kg; n=19) or placebo (n=20).
- Native T1 was acquired as an optional scan, the results of which are not reported here.
- MRI was conducted at baseline and Week 52 using a Philips or Siemens 3T system.

## RESULTS

### Table 1. Baseline clinical characteristics of EMBARK MR sub-study participants

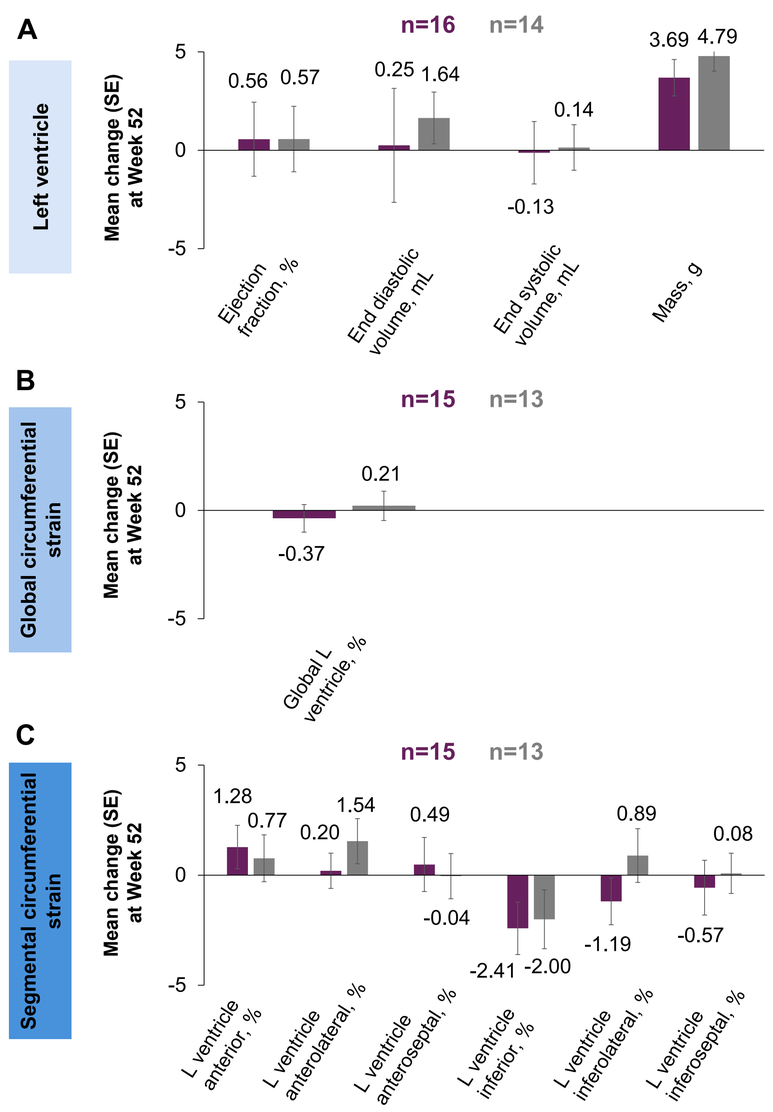
| Characteristic | Delandistrogene moxeparvovec (n=19) | Placebo (n=20) | All (N=39) |
|---|---|---|---|
| **Age, mean (SD), years** | 5.92 (1.10) | 6.27 (0.98) | 6.10 (1.04) |
| 4–5 years, n (%) | 10 (52.6) | 9 (45.0) | 19 (48.7) |
| 6–7 years, n (%) | 9 (47.4) | 11 (55.0) | 20 (51.3) |
| **Dosing weight, mean (SD), kg** | 22.44 (6.31) | 21.77 (5.94) | 22.09 (6.05) |
| **Time since corticosteroid treatment started, mean (SD), years** | 0.77 (0.53) | 0.91 (0.51) | 0.84 (0.52) |
| **Pathogenic variant, n (%)** | | | |
| Large deletion | 16 (84.2) | 13 (65.0) | 29 (74.4) |
| Small mutation | 3 (15.8) | 7 (35.0) | 10 (25.6) |
| **NSAA total score, mean (SD), points** | 23.61 (3.85) | 22.40 (3.58) | 22.99 (3.71) |
| **TTR, mean (SD), seconds** | 3.48 (0.98) | 3.46 (0.78) | 3.47 (0.87) |

### Table 2. cMRI findings at baseline and Week 52

| Parameter, mean (SD) | Baseline | | Week 52 | |
|---|---|---|---|---|
| | Delandistrogene moxeparvovec | Placebo | Delandistrogene moxeparvovec | Placebo |
| **Left ventricle** | | | | |
| Ejection fraction, % | 64.69 (6.04) | 64.58 (5.92) | 65.41 (5.44) | 66.29 (5.90) |
| End diastolic volume, mL | 50.88 (11.84) | 47.47 (11.10) | 50.88 (11.43) | 49.71 (11.74) |
| End systolic volume, mL | 18.13 (5.54) | 17.00 (5.11) | 17.82 (5.38) | 16.93 (5.41) |
| Mass, g | 39.56 (9.56) | 40.32 (10.52) | 43.47 (9.02) | 48.21 (10.31) |
| **Global circumferential strain** | | | | |
| Global L ventricle, % | –18.37 (2.89) | –18.59 (2.50) | –18.71 (1.87) | –18.53 (2.73) |
| **Segmental circumferential strain** | | | | |
| L ventricle anterior, % | –19.02 (4.14) | –18.80 (3.26) | –18.02 (4.32) | –18.76 (4.12) |
| L ventricle anterolateral, % | –19.24 (4.07) | –19.81 (2.92) | –18.97 (2.99) | –18.01 (3.12) |
| L ventricle anteroseptal, % | –17.68 (3.86) | –17.04 (3.40) | –17.29 (2.65) | –17.38 (2.25) |
| L ventricle inferior, % | –16.41 (3.23) | –17.69 (4.22) | –18.80 (3.22) | –19.45 (4.77) |
| L ventricle inferolateral, % | –21.45 (3.42) | –21.69 (3.60) | –22.29 (4.24) | –21.35 (5.27) |
| L ventricle inferoseptal, % | –16.40 (2.98) | –16.50 (3.21) | –16.92 (4.90) | –16.25 (3.31) |

- Patient demographics, clinical characteristics and cMRI findings at baseline were balanced between delandistrogene moxeparvovec and placebo groups (**Tables 1 and 2**).
- cMRI results remained similar between delandistrogene moxeparvovec and placebo groups at Week 52 (**Table 2**).

### Figure 2. Summary of cMRI findings at Week 52*




- At Week 52, analysis of cMRI **left ventricular parameters**, including ejection fraction, end diastolic volume, end systolic volume and mass, revealed no relevant differences between delandistrogene moxeparvovec and placebo in the sub-study population (**Figure 2A**).
- Analysis of the **global circumferential strain** of the left ventricle revealed no relevant differences between delandistrogene moxeparvovec and placebo at Week 52 (**Figure 2B**).
- Analyses of the **segmental circumferential strain** parameters across different regions of the left ventricle revealed no relevant differences between delandistrogene moxeparvovec and placebo at Week 52 (**Figure 2C**).

*cMRI findings are reported for patients with cMRI data available at both baseline and Week 52.

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## Abbreviations

α-MHC, alpha-myosin heavy chain; cMRI, cardiac magnetic resonance imaging; DMD, Duchenne muscular dystrophy; IV, intravenous; L, left; MR, magnetic resonance; MRI, magnetic resonance imaging; NSAA, North Star Ambulatory Assessment; rAAVrh74, recombinant adeno-associated virus rhesus isolate serotype 74; SD, standard deviation; SE, standard error; T1, longitudinal relaxation time; TTR, Time to Rise; vg, vector genomes.

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